

198 The Pancreas

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The pancreas is an elongated retroperitoneal gland in the upper abdomen that has both an exocrine and an endocrine component. The pancreas is divided into three parts: the head, the body, and the tail. The head lies in the C-shaped region of the duodenum, while the body and tail extend from the C-loop of the duodenum across the midline of the body toward the spleen. Pancreatic secretion empties through the pancreatic duct which merges with the common bile ducts into the duodenum via the ampulla of Vater.

In this chapter, the embryology, histology, ultrastructure, and development of the functions of the pancreas have been reviewed. In addition, the physiology of the pancreas, congenital diseases of the exocrine pancreas, and the evaluation of pancreatic function will be discussed. A detailed review of acute and chronic pancreatitis will also be provided.

Embryology

By the fifth week of gestation, the pancreas arises as two outpouchings from the junction of the foregut and midgut. The large dorsal bud enlarges rapidly and contributes to most of the pancreas. The small ventral bud contributes to the uncinate process and the inferior part of the head of the pancreas. The ventral bud, connected to the bile duct, rotates with the duodenum and fuses with the dorsal bud. By the seventh week of gestation, as the two buds join, the ventral duct fuses with the dorsal duct to form the main pancreatic duct (duct of Wirsung). This duct communicates with the common bile duct before entering the duodenum via the ampulla of Vater. The proximal portion of the dorsal duct forms the accessory duct of Santorini, which opens separately above the main papilla. Developmental deviation from these steps may result in clinically significant anomalies as will be discussed later. The pancreatic acini and the islets of Langerhans start developing during the third month of gestation.

Histology and Ultrastructure

The pancreas is composed of the exocrine system involved in digestion, and the endocrine system involved in

secretion of hormones such as insulin and glucagon. Histologically, the exocrine system consists of lobules composed of numerous acini lined with epithelial cells which contain zymogen granules. Each acinar gland is drained by a small ductule connected to larger ducts which in turn connect to the major pancreatic duct. The zymogen granules are secretory vesicles that release trypsinogen, chymotrypsinogen, procarboxypeptidase, amylase, and lipase for the purpose of food digestion.

The endocrine system consists of the islets of Langerhans, which are interspersed among the acinar glands. Three major cell types are recognized in these islets: Alpha cells produce glucagon, β -cells produce insulin, and γ -cells produce somatostatin.

Physiology of the Pancreas

The acinar cells secrete the enzymes responsible for the degradation of food, while the epithelial cells lining the pancreatic ducts secrete fluid and bicarbonate that render the duodenal lumen pH alkaline. This provides the optimal milieu for enzymatic activity.

Pancreatic exocrine secretions are under neural and hormonal control. The neural phase is mediated by vagal stimulation and results in the mobilization of enzymes from the acinar cells to the ducts. The hormonal phase is triggered by the passage of the acidic gastric contents into the duodenal lumen and results in the release of secretin from the duodenal mucosa. Secretin stimulates the secretion of bicarbonate and fluids. The hydrolytic products of proteins and fat stimulate the release of cholecystokinin (pancreozymin), bombesin, and neurotensin. These, in turn, stimulate the release of the pancreatic enzymes trypsinogen, chymotrypsinogen, procarboxypeptidase, amylase, colipase, and lipase.

The proteolytic enzymes (trypsinogen, chymotrypsinogen, and procarboxypeptidase) are released in their inactive form in order to protect the pancreas from autodigestion. Enterokinase, an intestinal brush border endopeptidase, activates trypsinogen to trypsin. Trypsin, in turn, activates chymotrypsinogen to chymotrypsin and procarboxypeptidase to carboxypeptidase. These

pancreatic enzymes are thus activated in the intestine where the digestive process takes place. Endopeptidases (trypsin, chymotrypsin, and elastase) cleave internal bonds within protein chains. Exopeptidases (carboxypeptidase A and B) cleave the bond adjacent to either the amino or carboxyl terminus. Pancreatic lipase is the principal enzyme needed for the hydrolysis of dietary triglycerides. Colipase is a pancreatic enzyme required to prevent the inactivation of lipase by bile salts. Amylase functions to hydrolyze starches into glucose oligomers and α -limit dextrins.

Development of Pancreatic Function

Studies in human fetuses have shown that zymogen granules are first detectable at a fetal length of 14 cm. The number and electron density of these zymogen granules increase as the fetus grows in length. Enzyme measurement of trypsin, chymotrypsin, lipase, and phospholipase are detected at about the same length, increasing slowly until the fetus reaches 40 cm in length. This is followed by a dramatic increase in enzyme activity. Amylase is absent in all fetuses.

In human infants between the ages of 1 day and 1 month, considerable amounts of proteases are found in duodenal fluids. The activity of carboxypeptidase B represents 10–25%, chymotrypsin 50–60%, and trypsin about 90–100%, respectively, of the activity levels found in children at the age of 2 years and older. Basal concentrations of lipase are barely detectable, and those of amylase are totally absent. Moreover, newborns are not responsive to pancreozymin stimulation at 1 month of age, with only a minimal increase in the output of chymotrypsin. Similarly, the response to secretin stimulation is minimal. A pronounced response is not seen until 2 years of age for both pancreozymin and secretin.

These findings clearly indicate that the infant's digestive capacity of fat and starch are less mature than those for proteins. Although lingual and breast milk lipase may compensate for the low levels of pancreatic lipase, low pancreatic-lipase levels may explain some of the transient malabsorption reported in infancy.

Anomalies of the Pancreas

Pancreas Divisum

Typically, anomalies of the pancreas represent failure of rotation or fusion, or both. Pancreas divisum results from

the failure of the ventral and dorsal pancreas to fuse, resulting in separate drainage systems for each bud. As a result, the majority of the exocrine pancreatic flow arising from the dorsal bud is drained by the smaller accessory duct of Santorini and the smaller accessory papilla. This is felt to represent an area of relative stenosis, potentially explaining the association of this anomaly with chronic pancreatitis in some clinical series. Other series, however, have failed to demonstrate a similar association.

In the clinical setting of recurrent pancreatitis, endoscopic and surgical approaches have been used for treatment of this anomaly, including sphincterotomy, stent placement, and pancreaticoduodenectomy. Pancreas divisum detected incidentally in the absence of pancreatitis should be treated expectantly.

Annular Pancreas

Annular pancreas results from a histologically normal pancreas partly or completely encircling the second part of the duodenum distal to the ampulla of Vater. The formation of the annulus is believed to result from the failure of the tip of the ventral pancreas to rotate completely to the right and posteriorly with the duodenum.

Annular pancreas is frequently associated with Down's syndrome, intestinal malrotation, tracheoesophageal fistulas, and congenital heart disease, especially tetralogy of Fallot.

In patients with a complete annular pancreas resulting in duodenal obstruction, presentation is usually in early infancy with bilious vomiting, abdominal distention, and a double bubble sign on plain abdominal films representing duodenal obstruction. If the annulus is incomplete, the patient may be asymptomatic or present later in life with intermittent abdominal pain or discomfort, epigastric fullness, nausea, and vomiting. Rarely, the annulus may compress the common bile duct or the pancreatic duct causing jaundice and/or pancreatitis.

In complete obstruction and in symptomatic patients, surgical intervention with a duodenostomy or duodenojejunostomy is the therapeutic procedures of choice.

Ectopic Pancreas

This is a relatively common developmental anomaly with an estimated incidence of 15%. The ectopic pancreas is found most commonly in the prepyloric region of the stomach, duodenum, and jejunum.

The composition of the ectopic pancreas is variable. It may show normal pancreatic tissue with acini, islets, and ducts, or it may be rudimentary, consisting only of a few ducts and acini. At endoscopy, the ectopic pancreas appears as a firm yellow nodule 0.5–4 cm in diameter with an umbilicated center.

Most patients are asymptomatic. However, it has been postulated that ectopic secretions may produce inflammation, spasm in the gut, and pain. Hemorrhagic ulceration and pyloric obstruction have been reported. The nodules may also act as a lead point for intussusception. In symptomatic patients, treatment is with simple surgical excision.

Evaluation of Pancreatic Function and Pancreatic Disease

Despite the large array of available tests for evaluating pancreatic function, the definitive diagnosis of pancreatic disorders is often difficult. This is particularly so because the pancreas has significant functional reserves. For example, it is estimated that loss of 99% of lipase and colipase activity is required before steatorrhea is observed. More sensitive tests are required to detect impairment, resulting in less than 98% loss of enzyme secretory capacity. It is therefore important to appreciate the capabilities and limitations of available tests.

Tests for Pancreatic Insufficiency

Stool examination for fat: A simple screening test for the presence of pancreatic insufficiency is examination of a stool smear, preferably stained with Sudan III, under a light microscope. This allows detection of undigested and neutral fat. This test is not reliable in mild steatorrhea. However, it serves as a crude test to identify patients who may need more accurate quantification of fat stool losses.

72-hour stool fat: The 72-h stool fat quantification represents a very reliable diagnostic test for steatorrhea. The pediatric patient is instructed to take at least 3 g/kg/day of dietary fat. Intake is documented and stools are collected over a 72-h period. Stool fat is then extracted. Excretion of more than 10% of ingested fat is abnormal in children older than 6 months, while excretion of more than 15% would be abnormal in infants less than 6 months of age.

Oral tolerance tests: This test consists of giving individuals a standard amount of fat (50 g), then measuring their serum triglycerides and chylomicron levels at

different time points (0, 2, 3, 5 h). Values are then compared to controls. To determine if an abnormality is a result of pancreatic disease, the test is repeated after the enteral administration of pancreatic enzymes.

Steatocrit: This novel concept of measuring stool fat has recently been proposed and requires further substantiation. In this test, a homogenized sample of stool is centrifuged at 15,000 rpm for 15 min in a hematocrit tube. Lipids separate to the top and are quantitated in a fashion similar to a hematocrit.

Measurement of trypsin and chymotrypsin activity in stool: Measurements of trypsin and chymotrypsin activity in stool are widely used to evaluate pancreatic exocrine function. A recently introduced photometric assay for chymotrypsin has improved the reliability of this method, with measurements correlating well with data for chymotrypsin from stimulated duodenal output. However, the sensitivity of this test is affected by bacterial proteases that may lead to the breakdown of trypsin and to a lesser extent, chymotrypsin.

Bentiromide: Bentiromide is a nonabsorbable synthetic peptide, which is cleaved in the upper small intestine by chymotrypsin to yield the rapidly absorbable compound, para-aminobenzoic acid (PABA). Assuming intestinal mucosal integrity, serum PABA levels would then reflect pancreatic exocrine function. Urine PABA levels can also be measured but rely on normal hepatic, renal, and intestinal function. Different modifications on this test have been introduced to improve its sensitivity.

Fluorescein dilaurate test: The principal behind this test is similar to that of Bentiromide. Fluorescein dilaurate is orally administered and is then subject to hydrolysis by pancreatic cholesterol ester hydrolase to yield water soluble Fluorescein. Fluorescein is rapidly absorbed by the intestine, conjugated in the liver and excreted by the kidney as Fluorescein diglucuronide. Either urine collected over a 10-h period or a serum sample collected at 4–5 h is assayed for Fluorescein diglucuronide. These levels would then indirectly reflect pancreatic exocrine function. Different modifications of this test have been introduced to improve its sensitivity and to eliminate any possible effects of the intestine, liver, and kidney on this assay.

Isotope-labeled breath test: The use of stable isotopes to label ingested triglycerides is gaining momentum. In this test, triglycerides are radiolabeled with ^{13}C , and labeled CO_2 excreted in breath is then measured. The appearance of ^{13}C in the breath is reflective of intraluminal digestion of lipids. This test may eventually be used as a screening test for steatorrhea to replace the 72-h fecal fat test. Specificity for pancreatic disease may be improved by

repeating the assay after enteral administration of pancreatic enzymes.

Measurement of serum pancreatic enzymes: Serum pancreatic enzyme determinations can be specific tests for pancreatic insufficiency in the absence of acute pancreatitis, ductal obstruction, or renal insufficiency. Serum determinations for amylase and lipase are unreliable during early infancy because these enzymes do not reach mature levels until 3–6 months of age. Trypsinogen is the serum pancreatic enzyme of choice for pancreatic exocrine function testing.

Pancreatic stimulation tests: The tests discussed thus far are only able to detect severe cases of exocrine pancreatic insufficiency, where the pancreas has little functional reserve. Assessment of pancreatic reserve in patients without overt malabsorption is achieved through direct stimulation tests. These techniques are valuable in determining pancreatic function in those patients with greater than 2% functional residual capacity. Here the pancreas is stimulated pharmacologically or nutritionally, and pancreatic secretions are collected and analyzed for output of ions, water, and enzymes. This technique involves intubating the duodenum with a double lumen tube. After the collection of baseline duodenal fluids, secretin and panceozymin are infused intravenously, followed by the collection of duodenal fluids at specific intervals. The fluid volume, fluid pH, and HCO_3^- and electrolyte concentrations are determined. The fluid is also assayed for activity of trypsin, lipase, and colipase.

Nutrient stimulation tests: This test follows the same principal as pharmacologic tests but utilizes physiologic stimulation of the pancreas via the intraluminal infusion of nutrients. These tests have several disadvantages, including contamination by gastric secretions, and interference of nutrient substances with accurate enzymatic determinations.

Biochemical Tests for Pancreatitis

Serum amylase: Measuring serum amylase level is one of the most commonly used biochemical tests in the diagnosis of pancreatitis. Serum amylase levels increase within 3 h of pancreatic inflammation and may persist for 2–4 days. There is no correlation between the degree of serum elevation of amylase, or other pancreatic enzymes, and the severity of pancreatitis. However, hyperamylasemia may be in association with impaired renal function, in patients with perforated gastric or duodenal ulcers, postabdominal surgery, alcohol poisoning, pancreatic duct obstruction, and salivary-glands

inflammation. On the other hand, normal amylase level may be seen in 20% of patients with acute pancreatitis.

The measurement of serum pancreatic isoamylase in the diagnosis of pancreatitis is a more useful test as it may help delineate the source of amylase.

Traditionally, measurement of urinary amylase clearance has been advocated because renal tubular reabsorption of amylase is decreased in pancreatitis. However, it does not provide any advantage over measurement of total serum amylase, except in the setting of macroamylasemia, which is a benign condition seen in 1% of healthy individuals. In the latter condition, serum amylase is conjugated with IgM and, therefore, cannot be excreted through the kidney. Urine amylase clearance would be normal in macroamylasemia.

Serum lipase: Increased serum lipase level is more specific for acute pancreatitis than serum amylase, and the specificity increases when the serum level increases by threefold. Similar to amylase, lipase can come from different sources such as lingual, gastric and breast milk. However, studies in animals have shown that serum lipase is mainly pancreatic in origin. The reabsorption of cleared lipase by kidney tubules may keep serum levels elevated as long as 14 days. There is no other source for serum lipase, except the pancreas.

Serum cationic trypsinogen: Serum cationic trypsinogen has been used as a sensitive diagnostic screening test, especially in newborns. Infants with cystic fibrosis usually have manifold elevation in serum trypsinogen level. These values usually decline during the first 7 years in patients with pancreatic insufficiency.

Other tests: Several other tests have been evaluated for the diagnosis of acute pancreatitis. However, none has been proven superior to amylase and lipase. In adults, several tests have shown to be useful in predicting severity, including C-reactive protein, phospholipase A, interleukin 6, SPINK-1, Trypsinogen activator Peptide (TAP), and TNF α receptor. Trypsinogen 2 has been shown to be useful in diagnosing pancreatitis secondary to ERCP.

Radiological Evaluation of the Pancreas

Plain radiography: Plain abdominal films in chronic pancreatitis may show calcification of the pancreas. In acute pancreatitis, radiographs may show generalized ileus or a localized “sentinel loop,” which is a loop of dilated jejunum in the midepigastrium or left upper quadrant adjacent to the pancreas. Radiographs may show the “colon cut-off sign” which represents distention of the transverse colon with collapse of the descending colon.

Barium studies: Barium studies of the gastrointestinal tract may show esophageal varices due to splenic vein thrombosis and portal hypertension. An extrinsic mass effect on the stomach and duodenum from an inflamed and swollen pancreas or from a pseudocyst can be seen in some patients. Duodenal loop changes consisting of mucosal edema, distention, and air-fluid levels are frequently seen. Other signs include inverted “3” sign (Frostberg sign) which can be seen in the middle of the duodenum with the middle apex of the “3” representing the origin of the pancreatic duct and curves resulting from the swollen pancreatic head. Another sign is the Poppel sign, defining widening of the duodenal loop with prominent duodenal mucosal folds and the sphincter of Oddi.

Ultrasonography: Abdominal ultrasonograms provide good visualization of the pancreas as well as associated organs such as the hepatobiliary system. In acute pancreatitis, ultrasonography may reveal increase in the size and/or reduced echogenicity of the pancreas compared with that of the liver. Other findings may poorly define borders, dilated pancreatic ducts, and pseudocyst. Ultrasonography has several advantages such as simplicity, lack of radiation, and wide availability. Drainage of pseudocysts can be also done with ultrasonography guidance. Disadvantages of ultrasonography include poor imaging due to overlying gas obscuring the pancreas and the fact that it is operator-dependent. In chronic pancreatitis, in addition to the findings seen in acute conditions, ductal dilatation and accentuated echoes due to calcification are frequently observed. Ultrasonography is also a very useful tool in detecting and following up on pseudocysts.

Computerized tomography: Computerized axial tomography (CT scans) can detect calcification and calculi not evident by other radiologic modalities. Findings on CT scans include diffuse enlargement in patients with acute pancreatitis, hemorrhagic necrosis, and traumatic damage. It can also distinguish between pseudocysts and phlegmons. Therefore, when an ultrasound is inconclusive, CT scans could contribute to the diagnostic evaluation of pancreatic disorders and their complications. The drawback of the use of CT in children with pancreatitis is the need for sedation. A normal CT does not rule pancreatitis as 20% of patients with acute pancreatitis have normal CT.

Magnetic resonance cholangiopancreatography (MRCP): Advances in magnetic resonance technology has allowed the development of MRCP which is an excellent modality for obtaining images of the pancreaticobiliary tree. This imaging technique poses several advantages, including lack of radiation and lower complication rate compared to ERCP. The main disadvantage is poor ability to diagnose

peripheral biliary tree in children. Most centers, including ours, have been relying on this imaging modality to diagnose structural abnormalities of the pancreaticobiliary tree in children. The use of MRCP has replaced ERCP as a diagnostic modality limiting the use of ERCP in cases in which MRCP has been inconclusive or when therapeutic intervention is needed, such as stone removal, or when papilotomy or stent placement are needed.

Endoscopic retrograde cholangiopancreatography (ERCP): This technique involves endoscopic intubation of the pancreatic and biliary ducts. Despite the lack of experience in performing ERCP in children, it may provide very valuable information in patients with chronic pancreatitis. It allows identification of partial or complete obstruction of the intrapancreatic portion of the common bile duct. It also detects areas of narrowing, dilation, and tortuosity, or the presence of intraductal stones. Pancreas divisum can also be identified. Other diagnostic evaluations include measurement of sphincteric and ductal pressures. Therapeutic interventions such as dilatation and sphincteroplasty can also be performed in addition to stone removal and pseudocyst drainage. ERCP can also provide guidance prior to surgical intervention. However, the procedure is technically difficult in small children. Complications of ERCP are not different from those in adults and include pancreatitis, pain-requiring analgesia, perforation, ileus, and fever.

Congenital Diseases of the Exocrine Pancreas

Shwachman–Diamond Syndrome

Shwachman–Diamond Syndrome (SDS) is an autosomal recessive disorder characterized by pancreatic exocrine dysfunction, bone marrow failure, skeletal abnormalities, and leukemia predisposition. Mutations in Shwachman–Bodian–Diamond Syndrome (SBDS) gene located on chromosome 7 account for 90% of patients. The gene product is a protein likely involved in accelerated apoptosis.

The hallmark of this disease is the association of exocrine pancreatic insufficiency, bone marrow hypoplasia, and bony changes. Several other features have been also reported (🔗 [Table 198.1](#)).

Exocrine Pancreatic Insufficiency

Most patients present with steatorrhea in the first year of life. However, residual pancreatic function may allow

■ Table 198.1

Feature of Shwachman–Diamond Syndrome

Exocrine pancreatic insufficiency	Recurrent infections
Short stature	Renal tubular defects
Bone marrow hypoplasia	Fatty liver
Skeletal abnormalities	Dental effects
Hirschsprung disease	Ichthyosis
Impaired neutrophil functions	Diabetes mellitus
Endocardial fibrosis	

some patients to go unnoticed for several years. Exocrine function is abnormal with lipase being more severely depressed than other enzymes.

The pancreas appears grossly lipomatous. Histologically, the acinar glands are scarce or absent and are replaced entirely by fatty tissue. The islets of Langerhans appear intact.

Bone Marrow Hypoplasia

Bone marrow abnormalities may occur in one or all three blood lines. Neutropenia can be recognized in up to 95% of the patients, thrombocytopenia in 70%, and anemia in 50%. Neutropenia is usually cyclic with some patients mounting leucocytosis in response to infection. In vitro studies show impaired neutrophil mobility and chemotaxis. Bone marrow aspirates reveal hypocellularity and maturational arrest. Otitis media, sinusitis, osteomyelitis, and skin infections may be seen. However, overwhelming sepsis is usually the leading cause of death in this disorder.

Skeletal Abnormalities

Metaphyseal dysostosis in the femur, tibia, and ribs is recognized in about 10–15% of patients. The hip is the most frequently affected site thus adversely affecting the child's gait. The pathogenesis of these bony lesions is poorly understood. Spontaneous and complete resolution of these lesions after puberty has been reported in some patients. Early features include thoracic dystrophy manifesting as short ribs with flared anterior end “cup deformities” which may result in narrowing of the thoracic cage, causing respiratory distress. Clinodactyly of the fifth finger is a frequent finding seen in up to 50% of affected individuals. However, the most frequent radiologic abnormality is delayed bone age.

Growth Retardation

Growth retardation is characteristic of this disease. While pancreatic enzyme replacement may improve weight gain, linear growth is usually not ameliorated. The severity of skeletal abnormalities also does not correlate with the retardation of height. Intrauterine growth retardation may occur, but in most patients, growth retardation manifests in the first year of life.

Diagnosis

SDS should be considered in any patient with malabsorption, hematologic or skeletal abnormalities, and negative sweat chloride test. Evaluation of pancreatic function by the pancreozymin-secretin stimulation test is the most sensitive test in evaluating pancreatic function. Patients with SDS characteristically show normal or slightly low bicarbonate levels with depressed or absent pancreatic enzymes. Blood counts reveal variable neutropenia, thrombocytopenia, and anemia. Bone marrow aspiration may show hypocellularity. Abdominal ultrasonography may reveal normal pancreatic size with fatty tissue infiltration. Bony films show the characteristic of metaphyseal dysostosis.

Treatment

Pancreatic enzyme replacement is usually effective in controlling steatorrhea and improving weight gain. However, it rarely influences linear growth. Pancreatic enzyme supplementation may be eventually discontinued because most patients achieve normal fat absorption with age. Fat-soluble vitamins supplementation is usually recommended. Patients with neutropenia require no treatment when asymptomatic. However, these patients should be treated

as immunosuppressed individuals when presenting with fever, and appropriate antibiotic therapy and cultures are indicated. Cyclosporin A has been found to be efficacious in treating aplastic anemia associated with this disorder.

Johanson–Blizzard Syndrome

Johanson–blizzard syndrome is an extremely rare ectodermal dysplastic disorder characterized by microcephaly, aplasia or hypoplasia of alae nasi, midline scalp defects, abnormal hair pattern, absence of permanent teeth, growth retardation, mental retardation, hypothyroidism, exocrine pancreatic insufficiency, Café au lait spots, genitourinary anomalies, congenital heart defects, thyroid dysfunction, imperforate or anteriorly displaced anus, and congenital deafness. This condition results from an autosomal recessive disorder. The molecular basis of this disorder has been recently defined as mutations in the ubiquitin protein ligase E3 component n-recogin1 gene (UBRI) located on chromosome 15q.

Isolated Enzyme Deficiencies

Enterokinase deficiency: Enterokinase, an enzyme secreted by duodenal mucosa, is responsible for activating trypsinogen to trypsin. Accordingly, enterokinase deficiency results in trypsin, chymotrypsin, and procarboxypeptidase deficiency. Patients present early in life with diarrhea, anemia, hypoproteinemia, and failure to thrive.

Treatment with exogenous enterokinase is highly effective in controlling symptoms and improving growth.

Trypsinogen deficiency: Trypsinogen is activated by intestinal enterokinase into trypsin, which in turn activates chymotrypsinogen and procarboxypeptidase into their active form. Therefore, trypsinogen deficiency results in protein malabsorption. The clinical manifestations of this disease are indistinguishable from enterokinase deficiency. Treatment requires pancreatic enzyme replacement and providing formulas composed of protein hydrolysate.

Lipase and colipase deficiency: Lipase and its cofactor, colipase deficiencies are rare but well-recognized causes of steatorrhea and failure to thrive. Treatment with pancreatic enzymes and a low fat diet are effective means of controlling symptoms.

Acute Pancreatitis in Childhood

Acute pancreatitis refers to acute pancreatic inflammation with return of pancreatic morphology and function to

normal between attacks. Hemorrhagic or necrotizing pancreatitis refer to severe disease with extensive pancreatic necrosis associated with life-threatening systemic manifestations.

Previously considered to be uncommon in the pediatric age group, acute pancreatitis has been recognized more frequently in recent years. The disease carries with it a high rate of morbidity and mortality. The disorder should be considered in children with abdominal pain and elevated pancreatic enzymes. Lack of awareness and a delay in diagnosis may contribute to these high rates. It is therefore essential to keep a high index of suspicion to allow the early diagnosis and management of acute pancreatitis.

Etiology

While alcoholism and biliary tract disease are the most common causes of pancreatitis in adults, drugs, abdominal trauma, and multisystem disease are recognized to be the major offenders in children. [Table 198.2](#) depicts the major causes of pancreatitis in childhood.

Trauma could be blunt, penetrating, or postsurgical. Some children may present immediately after the trauma with abdominal pain and vomiting, but in most cases, the presentation is delayed days to weeks, which makes the causal relationship between the trauma and pancreatitis uncertain. Child abuse is increasingly recognized as a cause of pancreatitis in toddlers and infants.

Many drugs are known to induce pancreatitis in all age groups. Corticosteroid-induced pancreatitis is known to be associated with a high mortality rate, probably related to the underlying disease process for which the steroids were given. Valporic acid has been strongly linked to acute pancreatitis, although the process is reversible upon withdrawal of the drug. With aggressive therapies that increase survival of children with malignancies, an increasing number of cases of pancreatitis induced by chemotherapeutic agents have been recognized.

Although mumps virus is the most frequent viral infection thought to be responsible for pancreatitis, several other viruses have been recently recognized as causative agents. These include coxsackie B₅ virus, EB virus, adenovirus, reovirus, and Hepatitis A and Hepatitis B viruses. Most viral-induced pancreatitis are of the interstitial variety that usually run a milder course than hemorrhagic pancreatitis.

Several metabolic disorders have been associated with acute pancreatitis, including hyperlipoproteinemia type I, IV, and V, hyperparathyroidism, diabetes mellitus, and cystic fibrosis. Recently, refeeding pancreatitis in

■ **Table 198.2**

Causes of acute pancreatitis in children

1. <i>Trauma</i> – blunt or penetrating
2. <i>Drugs and toxins</i> (a) <i>Anti-inflammatory agents</i> : Corticosteroids, salicylates, and indomethacin (b) <i>Chemotherapeutic agents</i> : L-Asparaginase, 6-mercaptopurine, and azathioprine (Imuran) (c) <i>Diuretics</i> : Furosemide, chlorothiazides, and ethacrynic acids (d) <i>Anticonvulsants</i> : Valporic acid and dilantin (e) <i>Antibiotics</i> : Tetracycline and sulphonamide (f) <i>Anticoagulants</i> (g) <i>Alcohol</i> (h) <i>Venom of Scorpions</i> (i) <i>Organophosphates</i>
3. <i>Infection</i> – Mumps, rubella, hepatitis A and B, coxsacki B, mycoplasma pneumonia, and bacterial sepsis
4. <i>Parasites</i> – Ascaris and hydatid cysts
5. <i>Anatomic anomalies</i> – Choledochal cyst, annular pancreas, anomalous insertion of common bile duct, pancreas divisum, and stenosis of ampulla of Vater
6. <i>Metabolic and nutritional disorders</i> – Hypercalcemia, hyperlipoproteinemia Type 1, IV & V, Diabetes mellitus, cystic fibrosis, high concentrations of intralipids, and refeeding of malnourished children
7. <i>Vascular diseases</i> – Systemic lupus erythematosus, hemolytic uremic syndrome, and Henoch-Schönlein purpura
8. <i>Biliary diseases</i> – Gall stones, choledochal cyst, and biliary tree anomalies
9. <i>Hereditary</i>
10. <i>Shock</i>
11. <i>Idiopathic</i> (25%)

malnourished children and pancreatitis associated with high concentrations of lipid emulsions have been recognized with increasing frequency. Patients with 3-hydroxy-3-methyl glutaryl-coenzyme A lyase (HMG-CoA lyase) deficiency who present with recurrent pancreatitis are successfully managed with a low leucine diet. Patients with HMG-CoA lyase deficiency usually present with a clinical picture indistinguishable from Reye's syndrome, which has also been shown to be associated with pancreatitis.

Anatomic malformations are frequently encountered in patients with recurrent, relapsing pancreatitis. One common example is stenosis of the ampulla of Vater, which is amenable to sphincteroplasty in most cases. Other

conditions include an annular pancreas, choledochal cysts, and anomalous insertions of the common bile duct.

Biliary disorders as a cause of pancreatitis are encountered much less frequently in children than in adults. However, a high index of suspicion is essential in high-risk groups, such as patients with hemolytic anemia who are susceptible to cholelithiasis and subsequent pancreatitis.

Pathophysiology

As mentioned earlier, pancreatitis has a variable etiology. However, the fundamental event that leads to the pathology in pancreatitis is the activation of pancreatic zymogen and initiation of enzymatic autodigestion of the pancreas. The mechanism by which these zymogens are activated within the pancreas is as yet not completely clear.

Studies in experimental animals have shown that the retrograde injection of activated proteolytic enzymes (trypsin, chymotrypsin, and elastase) in small amounts results in interstitial edema and, in larger doses, leads to extensive vascular damage, edema, and hemorrhage. Kallikrein, also activated by trypsin, liberates bradykinin and kallidin, both of which induce vasodilation and increase vascular permeability, ultimately leading to hypotension.

Phospholipase A contributes to the pathogenesis of pancreatitis in several ways. Studies in rats have shown that the injection of phospholipase A into the pancreatic duct results in severe pancreatic parenchymal necrosis indistinguishable from that seen in human pancreatitis. The lecithin of pulmonary surfactant can be a target for phospholipase A and may contribute to the adult-type acute respiratory distress syndrome encountered in severe cases of acute pancreatitis. Phospholipase A can also release histamine from mast cells and potentiate the refractory hypotension seen in acute pancreatitis.

Lipase, which is present in the pancreas in the active form, results in parapancreatic and peritoneal fat necrosis when released from the pancreas. Circulating lipase may lead to fat necrosis in skin, bone, and joints. Medullary fat necrosis may result in pulmonary or cerebral fat embolization with a catastrophic outcome.

Refractory hypotension and respiratory failure are the leading causes of death in severe pancreatitis.

Many factors may contribute to the hypotension, sometimes seen in acute pancreatitis. Recognized entities include the acute loss of plasma and blood into the peritoneum caused by disruption of the blood vessel integrity and by increased permeability and vasodilatation, resulting from kallikrein and histamine release.

Respiratory compromise ranges from mild hypoxia to full blown respiratory distress syndrome. Many factors are implicated in its pathogenesis, including pleural effusions, fat embolization, pseudocyst formation, and surfactant destruction by phospholipase A.

Hypocalcemia seen in acute pancreatitis is thought to result from the binding of calcium with fatty acids in the areas of fat necrosis.

Clinical Manifestations

Abdominal pain, nausea, and vomiting are the most common presenting symptoms of acute pancreatitis. Abdominal pain is usually constant and severe but may be mild and intermittent. Pain is usually localized to the epigastric region and may spread to the back, although some children may localize the pain to the periumbilical region or the right upper quadrant. The pain is aggravated by oral intake and not relieved by vomiting. The child may lie on his or her side and assume the knee-chest position. Other symptoms may include anorexia, nausea, and vomiting which may be bilious.

The physical exam may reveal a low-grade fever, tachycardia, and hypotension. The patient may be dyspneic with decreased breath sounds due to the presence of a pleural effusion. The abdomen is usually tender with some guarding, especially in the epigastric region. Bowel sounds may be normal, hypoactive, or completely absent in patients with advanced paralytic ileus. Subcutaneous fat necrosis may result in bluish discoloration of the skin in the flanks (Turner's sign) and the periumbilical area (Cullen's sign). Other manifestations include hematemesis, melena, abdominal mass, and coma.

Diagnosis and Laboratory Data

The diagnosis of acute pancreatitis rests on compilation of clinical features, laboratory findings, and imaging techniques. Careful medical history is mandatory with special emphasis on family history and history of trauma in order to define the cause of pancreatitis.

Pancreatic enzyme levels: The most common laboratory changes are elevated serum lipase, amylase, and trypsin levels, as well as an elevated renal amylase/creatinine clearance ratio (above 4 is abnormal). Keeping in mind the several clinical entities that may result in similar chemical derangements and correlating these data with the clinical findings and radiological studies is the correct approach to reaching an early diagnosis of this catastrophic disease.

Although measuring serum lipase level is the most commonly used test in the diagnosis of pancreatitis, 35% of cases of acute pancreatitis may be missed if serum amylase is the only test done.

Hypocalcemia: Hypocalcemia is usually seen in severe cases of acute pancreatitis and correlates with a poor prognosis.

Hyperglycemia: Hyperglycemia is frequently encountered in acute pancreatitis. This complication is believed to result from an insult to β cells in the islets of Langerhans. However, plasma cortisol/glucagon and growth hormone may also play a role. Glucose intolerance is usually transient; however, lifelong diabetes mellitus has resulted from viral infections of the pancreas, especially mumps and coxsackie virus.

Hyperlipidemia: Hyperlipidemia not only induces pancreatitis but may also result from the metabolic derangements induced by acute pancreatitis.

Hypoalbuminemia: Hypoalbuminemia may be seen in patients with acute pancreatitis as albumin is an acute phase reactant and may be also seen secondary to expansion of the intravascular compartment with fluids.

Hematologic disturbances: Mild leukocytosis with left shift and hemoconcentration may be seen in some patients. Rapid decline in hematocrit indicates hemorrhagic pancreatitis.

Plain abdominal films should be done in patients with acute abdomen in order to exclude other abdominal disorders. As mentioned earlier, plain films may provide helpful information and characteristic signs that can help establishing the diagnosis (see [Evaluation of Pancreatic Function and Pancreatic Disease](#)).

Chest film should be obtained to rule out diaphragmatic or pulmonary involvement such as pleural effusion or adult respiratory distress syndrome (ARDS).

Abdominal ultrasounds, or CT scans, may reveal an enlarged and edematous pancreas with reduced echogenicity. It may also show a pseudocyst in the vicinity of the pancreas.

Complications of Acute Pancreatitis

Pseudocysts is a common complication following acute pancreatitis and may develop in 16–50% of the patients. The lining of the pseudocyst is composed of fibrous or granulation tissue without an epithelial component. It is fluid filled with pancreatic juice, blood, and tissue debris. It may develop in the course of the acute attack or many weeks later. In contrast to pseudocysts associated with chronic pancreatitis in patients with acute pancreatitis, pseudocysts do not communicate with pancreas. The presentation is usually that of a prolonged course of acute pancreatitis with persistent nausea and

vomiting, and prolonged elevation of serum amylase and lipase. Ultrasounds or CT scans are diagnostic. Small pseudocysts will most likely resolve spontaneously. However, large cyst, those that last more than 6 weeks, and those with abscess formation require immediate drainage. Ruptured cysts may cause severe and life-threatening chemical peritonitis.

Other complications such as respiratory, renal and hepatic failure, and refractory hypotension correlate with severe disease and a grave outcome.

There is no available data regarding mortality rate following acute pancreatitis in children. In adults, mortality rate is usually 9% per attack. On the other hand, the mortality rate following hemorrhagic and necrotic pancreatitis ranges between 15% and 50%.

Treatment

Treatment of acute pancreatitis is primarily supportive. The treatment should be directed toward the cause whenever identified. Other than avoiding the precipitating factors, maintaining intravascular volume, the mainstays of therapy are minimizing the stimulation of pancreatic exocrine secretions and pain management.

Almost all patients will have some degree of dehydration due to decreased intake, vomiting, leakage of intravascular fluids to the peritoneum, or hemorrhage. Based on the degree of dehydration, patient will require replacement of deficits, ongoing losses, and maintenance fluids. Caution should be applied in order to avoid fluid overload, which may result in pulmonary edema and congestive heart failure commonly seen 3–7 days from the onset of pancreatitis. Potassium should not be added to intravenous fluids before establishing acceptable urine output as renal failure may be seen in 2% to 17% of patients with acute pancreatitis. Monitoring electrolytes, including calcium and magnesium, is mandatory. If shock and hemorrhage are present, fresh frozen plasma or blood may be required. Treatment with intravenous pressor agents may be needed if these measures have failed in improving blood pressure. H₂ blocker or proton pump inhibitors may help reduce duodenal acidity and prevent gastritis and ulcer formation.

Complete bowel rest and employing gastric suction will reduce the dietary and hormonal stimulation of the pancreas. Oral feedings should not be resumed until pain and ileus have resolved and amylase normalized. When oral feedings are resumed, carbohydrates should be introduced first, avoiding fats and proteins in order to decrease pancreatic stimulation. If the patient requires prolonged

therapy, total parenteral nutrition is in order. In the past, anticholinergic drugs were frequently used to suppress the neural stimulation of pancreatic secretions. However, controlled studies have failed to prove their efficiency.

Adequate pain relief is essential. This can be accomplished with meperidine. Opiates should be avoided because they may cause spasm of the sphincter of Oddi. Persistence of pain beyond 2 weeks may indicate the development of pseudocyst, and ultrasound is usually recommended every few days to detect to monitor for this complication.

Prophylactic antibiotics are not recommended since studies have failed to substantiate their efficacy in preventing secondary infection.

Many patients with pancreatitis may have some degree of hypoxia which requires oxygen administration. With respiratory failure, ventilatory support may also be required. Thoracentesis may help in relieving the respiratory compromise resulting from pleural effusions.

Surgical intervention is usually reserved for treatment of complications of the disease or for the correction of underlying anomalies.

Chronic Pancreatitis

Chronic pancreatitis is a chronic inflammatory process with progressive and permanent damage to the structure and function of the pancreas. The disease is uncommon in childhood; however, it is encountered frequently enough to require a high index of suspicion.

Etiology of Chronic Pancreatitis

There are numerous causes of chronic pancreatitis. Hereditary or familial pancreatitis is an autosomal-dominant disease with incomplete penetrance, recognized mainly among whites in Europe and North America, and among Chinese children. The onset of this disease is usually in the second decade of life. Several mutations have been described such as mutations in the cationic trypsinogen (PRSS1) gene. In addition, mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) and the serine protease inhibitor Kazal type 1 (SPINK1) genes are also associated with pancreatitis.

Juvenile tropical pancreatitis inflicts young people in the tropics, where low protein staples are commonly consumed. The largest series has been reported from the southern Indian state of Kerala. It is also recognized in Zaire, Nigeria, Uganda, South Africa, and Malaysia.

The disease has been strongly linked to protein calorie malnutrition, although conclusive data is lacking.

Chronic pancreatitis may also result from obstructive processes usually arising from congenital anomalies. These include stenosis of the papilla of Vater, choledochal cysts, an annular pancreas, and pancreas divisum.

Chronic pancreatitis also arises from systemic and metabolic disorders, including hypercalcemia, hyperparathyroidism, hyperlipidemias, alpha-1-antitrypsin deficiency, cystic fibrosis, and inflammatory bowel disease.

Biliary disorders such as cholecystitis, cholelithiasis, and sclerosing cholangitis may also lead to chronic pancreatitis.

Chronic pancreatitis also results from extensive necrosis and fibrosis following an episode of acute pancreatitis.

Idiopathic chronic pancreatitis requires the exclusion of recognizable causes.

Clinical Presentation

The most common initial presentation of chronic pancreatitis is a clinical picture suggestive of repeated episodes of acute pancreatitis. Approximately one-half of patients present initially with episodes of acute pancreatitis. The other half will present with insidious pain, and a small percentage of patients will have no pain at all. Therefore, the majority of children with chronic pancreatitis have either intermittent or chronic abdominal pain lasting for weeks. The pain is localized to the epigastrium, the upper abdominal quadrants, the back, or occasionally the periumbilical area. As the disease progresses, the pain may diminish. Patients with chronic pancreatitis usually present between 10 and 12 years of age. By the age of 20 years, 75% of the patients are symptomatic. Males and females are equally affected. The diagnosis of chronic pancreatitis should be considered in patients presenting with obstructive jaundice, malabsorption, and diabetes.

Some patients may present with obstructive jaundice, with or without abdominal pain, secondary to narrowing of the distal common bile duct due to extensive fibrosis.

Exocrine insufficiency with steatorrhea and failure to thrive can be the presenting symptom in up to 20% of patients. Pancreatic exocrine failure could result from destruction of more than 98% of pancreatic acini or from obstruction of pancreatic ducts.

Glucose intolerance with hyperglycemia and glucosuria are common in the early stages of the disease. As the disease progresses, lifelong diabetes mellitus may develop, particularly in calcifying pancreatitis and tropical pancreatitis.

There have been numerous reports of pancreatic malignancies in some etiologic subgroups of patients

with chronic pancreatitis. Nonpancreatic malignancies are also reported in patients with familial pancreatitis.

Splenic vein thrombosis has been reported in chronic pancreatitis secondary to perivenous inflammation. Gastric varices secondary to splenic vein thrombosis is a common finding in patients.

Diagnosis

(See [Evaluation of Pancreatic Function and Disease](#))

The same diagnostic tests used in acute pancreatitis also apply to chronic pancreatitis. However, it is important to recognize that serum amylase and lipase may be normal or decreased in advanced cases due to pancreatic insufficiency. Pancreatic function evaluation with pancreozymin-secretin stimulation is a very valuable tool in assessing the degree of compromise in pancreatic exocrine function. Malabsorption may cause fat-soluble vitamin deficiency. Serum vitamin D and vitamin E carotene level and essential fatty acids may be decreased with prolongation of prothrombin time. Endoscopic retrograde cholangiopancreatography (ERCP) is the most sensitive diagnostic test in chronic pancreatitis. However, normal studies do not exclude the existence of pancreatitis.

Therapy for Chronic Pancreatitis

In the management of acute episodes of chronic pancreatitis, the same measures taken in acute pancreatitis are applied.

Management of malabsorption is also important. Fat intake should be limited while providing adequate protein and calories for growth. Use of medium chain fatty acids for improved absorption may be required. Continuous nasogastric alimentation with elemental formulas may be necessary in some patients. Pancreatic enzyme supplementation will also result in improvement of steatorrhea. Since lipase is inactivated in acidic pHs, gastric acid blockade with H₂-blockers or proton pump inhibitors can lead to increased bioavailability of pancreatic enzyme supplements. Patients may need insulin therapy with the development of diabetes mellitus.

Management of pseudocysts requires surgical internal or external drainage. Surgical therapy or ERCP-directed therapy is indicated for patients with intractable pain and for patients with obstruction of the common duct. ERCP can drain pseudocysts and allow removal of intraductal stones, placement of drains and stents, in addition to performing sphincterotomy. For definitive drainage of

the pancreas, a pancreaticojejunostomy may be required. In some patients, a partial or subtotal pancreatectomy may be required. With complete common bile duct obstruction, a choledochojejunostomy may be indicated. Pancreatic transplantation has recently become available, but experience in children is limited.

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